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Age-Related Changes of Urine Calcium Excretion after Extracorporeal Shock Wave Lithotripsy due to Artificial Renal Calcium Leakage

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Key Words
Renal stones · Lithotripsy · Renal function · Calcium

Abstract
Introduction: Extracorporeal shock wave lithotripsy (ESWL) is the standard stone treatment. Increased excretion of tubular enzymes and hypercalciuria has been reported after ESWL. We investigated the importance of renally induced hypercalciuria after ESWL. ***Material and Methods:*** 30 calcium oxalate stoneformers (23 men, 7 women), mean age 53.3 (range 30–71) years, were evaluated prospectively. Plasma calcium and creatinine concentrations and 8-hour overnight urine were measured before ESWL and on the 1st and 2nd days after ESWL. To estimate the changes of tubular reabsorption, the calcium/creatinine clearance ratios were calculated. ***Results:*** Hypercalciuria (>5 mmol/24 h) was seen in 5/30 (16.7%) before, in 12/30 (40.0%) on day 1 and in 13/30 (43.3%) on day 2 after ESWL. The mean plasma levels of calcium were significantly decreased from 2.36 mmol/l before to 2.28 mmol/l on day 2 after ESWL ($p < 0.01$). The mean calcium/creatinine clearance ratio was significantly increased from 0.012 before to 0.019 after ESWL ($p < 0.01$). Before and on day 2 after ESWL, the calcium/creatinine clearance ratio was significantly correlated with the age of the patients ($r = 0.33$, $p < 0.04$). ***Conclusion:*** Our data show an age-related significantly increased urine calcium excretion after ESWL possibly due to decreased tubular calcium reabsorption.

Objectives

Extracorporeal shock wave lithotripsy (ESWL) alone is the treatment of choice for approximately 90–95% of all stone-forming patients, or in combination with other procedures in the remaining stone patients. Depending on the size, location and composition of the stones and the anatomic abnormalities of the collecting system, the presence of residual stone material after ESWL is common [1, 2]. An increase in stone formation and the growth of residual fragments after lithotripsy due to urine hypersaturation has been reported [3].

Changes in renal function after ESWL have also been documented, with increased tubular enzymes, glomerular protein excretion in urine and hypercalciuria seen from 1 up to 5 days after primary ESWL [4–7]. The tubular damage may be explained by ischemic anoxia of tubular cells after lithotripsy and induced bleeding of the renal parenchyma, followed by generation of free radicals and lipid peroxidation resulting in toxicity to tubular cells [8].

The tubular epithelium plays an important role in renal calcium clearance. After the glomerular filtration of about 60% of plasma calcium, only 1–2% of the filtrated calcium is eliminated with the urine because of a highly specific tubular reabsorption process [9]. The calcium/creatinine clearance ratio (Ca/CrCl ratio) strongly correlates with the tubular function of calcium reabsorption. Ca/CrCl ratios of 0.01 are associated with normal renal

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Table 1. Stone size, stone location, applied shock waves and stone analysis of the treated patients

Mean stone size	8.9 × 7.4 (± 4.8) mm
Caliceal stones	20 patients
Renal pelvic stones	10 patients
Mean applied shock waves	2,681 (± 849) waves

tubular function [10]. Thus, tubular shock wave-induced damage might correlate with changes of renal clearance of calcium. We investigated the clinical importance of renally induced hypercalciuria in calcium-oxalate stone-formers after primary ESWL.

Materials and Methods

In a prospective study, 30 calcium-oxalate-forming patients (23 men, 7 women) were evaluated. The mean age of the patients was 53.3 ± 12.4 years. All patients had normal creatinine clearance, normal intravenous pyelograms and normal serum values of parathyroid hormones. The urine was sterile in all patients. The ESWL was performed with the lithotriptors MFL 5000 and Siemens Multiline. Stone size, stone location, applied shock waves and stone analysis of the treated patients are given in table 1. Urine samples from 8-hour overnight collection (10 p.m. to 6 a.m.) were measured before ESWL and on day 1 (up to 18 h after ESWL) and day 2 (up to 42 h after ESWL). The measurements from the urine samples were extrapolated to a 24-hour value. Fluid intake was not restricted. Patients received the normal hospital diet and recorded their daily dietary intake (table 2).

Means were compared by Wilcoxon's test and correlation were calculated by Pearson's correlation coefficient.

Results

Hypercalciuria (>5 mmol/24 h) was seen in 5/30 (16.7%) patients before ESWL, in 12/30 (40.0%) on day 1 (up to 18 h after ESWL) and in 13/30 (43.3%) on day 2 (up to 42 h after ESWL) (table 3). There were stable creatinine clearance values after ESWL in comparison to the values before (table 4). The mean values of calculated 24-hour urine calcium excretion increased significantly from 3.57 mmol/24 h before ESWL to 5.09 ± 3.0 mmol/24 h on day 1 ($p < 0.01$) and to 5.23 mmol/24 h on day 2 after ESWL ($p < 0.01$; table 3). Mean plasma levels of calcium were significantly decreased from 2.36 mmol/l before ESWL to 2.28 mmol/l on day 2 after ESWL ($p < 0.01$). The mean calcium/creatinine clearance ratio was significantly increased from 0.012 before ESWL to 0.019 after ESWL ($p < 0.01$; table 4). A significant correlation of the calcium/creatinine clearance ratio with age was seen before ESWL ($r = 0.33, p < 0.037$) and on day 2 after treatment ($r = 0.33$, $p < 0.040$) (fig. 1).

Table 2. Daily dietary intake of the patients with the code of diet

Patient No.	Day before ESWL	Day of ESWL	1st day after ESWL
1	1	3	5
2	1	2	5
3	4	2	4
4	4	3	5
5	1	3	5
6	1	1	5
7	4	3	5
8	4	3	5
9	1	3	5
10	1	3	5
11	5	3	5
12	1	2	5
13	1	2	5
14	1	3	5
15	1	2	5
16	2	1	1
17	1	2	5
18	4	2	1
19	5	3	1
20	1	2	2
21	5	6	5
22	3	5	1
23	5	6	5
24	5	6	5
25	4	6	5
26	6	3	5
27	5	5	6
28	1	3	5
29	1	3	1
30	1	3	1

The diet codes following are given in the order breakfast/lunch/dinner. 1 = Continental breakfast/soup/soup; 2 = fasting/fasting/fasting; 3 = fasting/fasting/dinner; 4 = continental breakfast/lunch/soup; 5 = continental breakfast/lunch/dinner; 6 = fasting/lunch/dinner.

Discussion

ESWL, due to the high efficiency and low morbidity rate of the HM3 lithotriptor, became the treatment of choice for most renal stones after 1980 [11]. With the high number of residual fragments after primary ESWL,

Table 3. Plasma calcium and calculated 24-hour calcium urine excretion (mean ± SD)

	Plasma calcium mmol/l	Calcium in urine mmol/24 h
Before ESWL	2.36 ± 0.12	3.57 ± 2.3
1st day (18 h) after ESWL	2.32 ± 0.10	5.09 ± 3.0**
2nd day (42 h) after ESWL	2.28 ± 0.10*	5.23 ± 3.3**

Wilcoxon's test comparing the values before and after ESWL. * $p < 0.05$, ** $p < 0.01$.

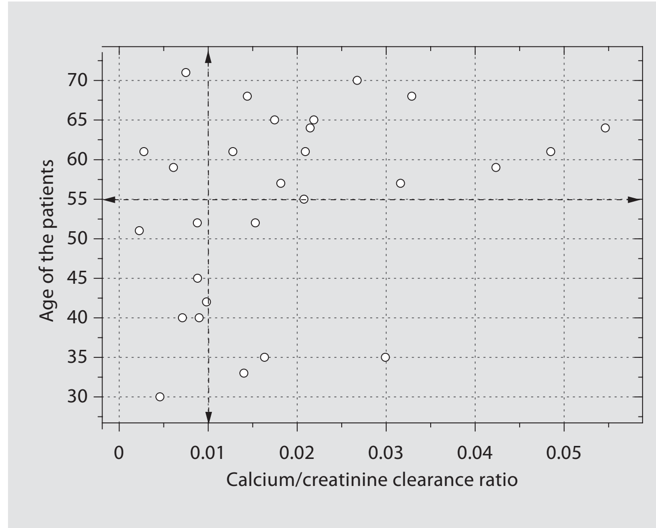

Fig. 1. Scatter plot with correlation between the age of the patients and the calcium/creatinine clearance ration 42 h after ESWL ($r = 0.33$; $p < 0.04$; Persons' correlation coefficient).

Table 4. Urine volume, creatinine clearance and calcium/creatinine clearance ratio (mean ± SD)

	Urine volume ml	Creatinine clearance ml/min	Calcium/creatinine clearance ratio
Before ESWL	579 ± 372	77.4 ± 23.6	0.012 ± 0.007
1st day (18 h) after ESWL	974 ± 573*	78.3 ± 30.7	0.019 ± 0.011*
2nd (42 h) after ESWL	815 ± 350*	79.8 ± 30.0	0.019 ± 0.014*

Wilcoxon's test comparing the values before and after ESWL. *$p < 0.01$.

further treatment or other measures are needed to render the patients stone free [3, 12–14]. Retreatment rates after primary ESWL are significantly correlated with stone burden and location. Stone-free rates are about 63, 73 and 71% for lower, middle and upper caliceal stones [15].

In our study, early significant changes in the 8-hour overnight urine collection after ESWL were measurable under conditions of a nonstandardized diet. The number of calcium-oxalate stoneformers with pathological calcium urine excretion increased significantly from 5/30 before ESWL to 13/30 42 h after ESWL in the study group. With a stable creatinine clearance after ESWL, the calcium/creatinine clearance ratios were significantly increased indicating decreased tubular reabsorption. The calcium plasma levels were also significantly decreased over the investigated period. Hypercalciuria due to higher oral calcium intake therefore appears to be unlikely. Thus, it seems that tubular dysfunction after ESWL leads to hypercalciuria because of a decreased tubular reabsorption of the filtrated calcium.

Several studies have demonstrated that an oral citrate treatment after ESWL can decrease the regrowth of residual fragments. These studies showed a 75% reduction in size in residual fragments and a 28.5% reduction in stone recurrences under treatment with oral citrate [16, 17]. Oral citrate elevates urinary pH values, reduces calcium excretion, inhibits the urine calcium binding capacity and increases the urinary citrate excretion. Therefore, calcium oxalate stone forming patients who can be expected to undergo repeated lithotripsy for a large stone mass might benefit from early metaphylaxis with oral citrate treatment in order to reduce the early regrowth of residual fragments related to ESWL-induced hypercalciuria.

The tubular effects as expressed by hypercalciuria were more pronounced in older than in younger patients. In our study, patients over 55 years of age had a higher risk for post-lithotripsy hypercalciuria. Concerning ESWL-induced tubular damage, Strohmaier et al. [18] demonstrated that calcium antagonists (e.g. nifedipine) produce a protective effect. In conclusion to our data, patients over 55 years seem to have more benefit from protective agents to reduce the tubular damage after ESWL. Our findings might also be of relevance for the timing of ESWL retreatment as these should be done after the restoration of normal tubular function [4, 16].

Conclusions

Our data show a significantly increased urinary calcium excretion, with potential implications for early metaphylaxis in calcium oxalate stone-forming patients after primary ESWL. Furthermore, age-dependent damage of tubular renal function was seen, which might be of relevance for the timing of ESWL retreatment and the use of protective tubular agents for patients over 55 years.

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